III. RESPONSE TO OFFICE ACTION

A. State of the Claims

At the time of the Action, claims 38-40 and 52-99 were pending. Claim 100 has been added. Claims 38, 52, 62, and 67 have been amended. Claims 76-99 have been canceled. Therefore, claims 38-40, 52-75 and 100 are currently pending. For the convenience of the Examiner, a copy of the pending claims is attached hereto as Exhibit A.

B. The Sequences in Figure 14 Will Be Added by Amendment

The sequence listing filed September 15, 1999 does not contain the sequence for J-Toll 4 shown in FIGS. 7A-7B. The sequence listing also does not contain the sequences provided in the description of FIG. 14 at page 18, line 7, 9, 14 and 17. An amended sequence listing which includes these sequences is in preparation and will be filed in the immediate future.

C. The Pending Claims are Enabled.

All of the pending claims, save claim 100, are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants respectfully traverse this rejection.

The Action acknowledges that there is enablement for "screening methods which modulate a LPS mediated response by inducing the synthesis or altering the activity of TLR-4 of SEQ ID Nos:2, 4, 6, 98 and 99." The Action indicates that there is no enablement for "other methods of screening for compounds which may affect any other LPS-mediated responses or methods for identification of compounds which may predictably have other activities by any way other means than the altered expression of TLR-4 (SEQ ID Nos:2, 4, 6, 98 and 99)."

The pending claims are directed to methods of screening for modulators of a lipopolysaccharide mediated response that compare the activity of a TLR-4 polypeptide before and after contact with a putative modulator or candidate substance. Therefore, the rejection

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appears to be aimed at limiting the methods to use of only five of the specific sequences disclosed. However, the scope of Applicants' invention is not so narrow. Claims need not be limited to exemplification or preferred embodiments in order to satisfy enablement requirements." *Ex parte Gould,* 6 U.S.P.Q.2d 1680 (B.P.A.I. 1987). "Enablement is not precluded by the necessity for some experimentation...However, experimentation needed to practice the invention must not be undue experimentation. The key word is undue, not experimentation. The determination of what constitutes undue experimentation in a case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art." *In re Wands*, 858 F.2d 731 (Fed.Cir. 1988). Given the nature of the present invention, the amount of experimentation to select other TLR-4 polypeptides for use in the methods of the claimed invention is not unreasonable. One of ordinary skill in the art can readily practice the claims of the present invention without resort to undue experimentation. Therefore, Applicants respectfully request the withdrawal of this rejection.

D. The Claims are Definite Under 35 U.S.C. § 112, Second Paragraph.

All of the pending claims were rejected under 35 U.S.C. § 112, second paragraph as indefinite.

As suggested by the Action, the claim term "LPS" has been changed to "lipopolysaccharide." Claim 38 has been amended to clarify how the goal of screening for modulators of a LPS mediated response is obtained. Claim 62 has been amended to provide proper antecedent basis for the "nucleic acid segment" term. The Markush grouping in claim 67 has been amended, eliminating the cause of the Action's rejection of this claim. Claim 52 has been amended, mooting the rejection of this claim as indefinite. Support for the amendments may be found throughout the Specification.

The Action indicates that "TLR-4" has not been sufficiently defined in the claims and specification (with respect to claims 38, 52, 55, 56, and 62-64). However, Applicants direct the Examiner to the Specification at page 6, lines 2-5, which states:

> "Recently the nomenclature for the Toll-4 protein has been changed to TLR-4 (Toll-like receptor 4). Thus, in the context of the present invention it is important to note that Toll-4 and TLR-4 are used interchangeably. The new nomenclature will be used herein, unless such designation leads to ambiguity in certain textual embodiments."

Applicants therefore urge that "TLR-4" has been defined adequately to meet the requirements of 35 U.S.C. § 112, second paragraph.

The Action also states that "TLR-4 polypeptide" is not an art accepted term and does not provide any structural or functional properties of the polypeptide (with respect to claim 38). Applicants disagree. For example, Hoshino et al. state that "human homologues of *Drosophila* toll, termed Toll-like receptors (TLR), have been cloned, and it is implicated that they activate both innate and adaptive immune responses in vertebrates...Recent genetic and physical mapping of the *Lps* locus identifies TLR4 as a candidate gene in the critical region." Hoshino et al., *J. Immunology* 162:3749-3752 (1999), Exhibit B. Qureshi et al. noted that there was strong support for the hypothesis that altered "Toll-like receptor 4 (*Tlr4*), part of a protein family with members that have been implicated in LPS-induced cell signaling," is responsible for endotoxin tolerance. Qureshi et al., *J. Exp. Med.* 189(4):615-625 (1999), Exhibit C. In addition, at page 5, lines 23-24 of the Specification is found the statement "the Toll-4 or TLR-4 polypeptide plays a role as the LPS receptor." This statement clearly indicates a functional property for the TLR-4 polypeptide. Thus "TLR-4 polypeptide" is a term recognized in the art which provides structural and functional properties of the polypeptide.

With respect to claims 38 and 40, the Action claims that it is not clear what the term "standard activity profile" means, what it measures, and how it is assayed. The Specification states that "[t]he present invention provides methods of screening for modulators of LPS mediated response by monitoring the standard activity profile of TLR-4 in the presence and absence of the candidate substance and comparing such results." Specification, p. 78, lns. 12-14. In further explanation the Specification states:

> "The candidate screening assays are simple to set up and perform. Thus, in assaying for a candidate substance, after obtaining a cell expressing functional TLR-4, one will admix a candidate substance with the cell, under conditions which would allow measurable TNF secretion to occur. In this fashion, one can measure the ability of the candidate substance to stimulate the TNF secretory response of the cell in the absence of the candidate substance. One would then measure the response in the presence of the candidate substance and determine the effect of the candidate substance....
>
> Significant changes in inflammatory response, *e.g.*, as measured TNF production, splenocyte activity and the like are represented by an increase/decrease in the response of at least about 30%-40%, and most preferably, by changes of at least about 50%, with higher values of course being possible."

Specification, p. 80, lns. 8-14 and 20-23. As indicated above, examples of assays that fall within the "standard activity profiles" contemplated by Applicants include splenocyte proliferation assays and macrophage response assays (TNF production by peritoneal macrophages). Details of these assays are disclosed in the Specification at page 87, line 9 to page 88, line 15. In addition, in some embodiments of the invention, "[t]he standard activity profile of the TLR-4 polypeptide is determined by determining the ability of the TLR-4 polypeptide to stimulate transcription of a reporter gene, the reporter gene operatively positioned under control of a nucleic acid segment comprising a promoter from a TLR-4 gene, the reporter gene operatively positioned under control of a nucleic acid segment comprising a promoter from a TLR-4 gene." Specification, p. 10, lns. 10-13. Such methods are well known by those of ordinary skill in the

art. Applicants contend that the above information provides adequate definition of the term "standard activity profile" to be definite under 35 U.S.C. § 112, second paragraph.

Claim 77 is said to be indefinite because it is not clear how the "change in the activity of TLR-4 polypeptide contacted with the candidate compound substance is related to the standard activity profile." Although claim 77 has been deleted, Applicants wish to address this rejection, because claim 38, as amended, contains language similar to that found indefinite by the Action. Claim 77 recites the conclusion "wherein a change in the activity of the TLR-4 polypeptide contacted with the candidate substance, when related to the standard activity profile, indicates that said candidate substance is a modulator of an LPS mediated response." Claim 38 recites the conclusion "wherein a difference in the standard activity profiles indicates that the putative modulator is a modulator of a lipopolysaccharide mediated response." The Specification discloses screening for modulators of LPS mediated response by monitoring the standard activity profile of TLR-4 in the presence and absence of the candidate substance and comparing such results, indicating that "this screening technique will prove useful in the general identification of a compound that will serve the purpose of promoting, augmenting or increasing the activity of TLR-4 of a macrophage cell." Specification, p. 79, lns. 12-16. The Specification further discloses that "in assaying for a candidate substance, after obtaining a cell expressing functional TLR-4, one will admix a candidate substance with the cell, under conditions which would allow measurable TNF secretion to occur. In this fashion, one can measure the ability of the candidate substance to stimulate the TNF secretory response of the cell in the absence of the candidate substance. One would then measure the response in the presence of the candidate substance and determine the effect of the candidate substance." Specification, p. 80, lns. 8-14. Two particular assays, a splenocyte proliferation assay and a macrophage response assay, are disclosed.

Specification, p. 87, ln. 8 to p. 88, ln. 15. Therefore, the language of claim 77 (and claim 38) questioned by the Action is sufficiently definite to comply with the statutory requirements. *In re Moore and Janoski,* 439 F.2d 1232 (C.C.P.A. 1971) ("In determining whether claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity, the definiteness of the language employed must be analyzed—not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.")

In addition, the Action states that "it is not clear what LPS mediated response is measured" (with respect to claims 38 and 77). As stated above, the Specification discloses "in assaying for a candidate substance, after obtaining a cell expressing functional TLR-4, one will admix a candidate substance with the cell, under conditions which would allow measurable TNF secretion to occur. In this fashion, one can measure the ability of the candidate substance to stimulate the TNF secretory response of the cell in the absence of the candidate substance." Specification, p. 80, lns. 8-12. In the section of the Specification titled "Assays for LPS responsiveness" two examples of LPS-mediated response assays are described: a splenocyte proliferation assay and a macrophage response assay. Specification, p. 87, ln. 8 to p. 88, ln. 15. The splenocyte response assay compares the proliferation of splenocytes incorporating tritiated thymidine (as measured by counts per minute, CPM) with and without stimulation with LPS. The macrophage response assay measures the per cent of cytotoxicity due to TNF released by cells in response to LPS. The information disclosed in the Specification regarding "LPS mediated response" meets the definiteness requirements of 35 U.S.C. § 112, second paragraph.

Claim 38 is said to be indefinite because it is not clear "what method steps are used to obtain a TLR- polypeptide" in this claim. However, as stated in the Specification at page 27,

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lines 5-11:

> "TLR-4 may be obtained according to various standard methodologies that are known to those of skill in the art. For example, antibodies specific for TLR-4 may be used in immunoaffinity protocols to isolate TLR-4 from cells. Antibodies are advantageously bound to supports, such as columns or beads, and the immobilized antibodies can be used to pull the TLR-4 target out of the cell lysate. Size fractionation (chromatography, centrifugation), ion exchange or affinity chromatograph, and even gel purification may be used for purification as well."

According to the Federal Circuit "[a] patent need not teach, and preferably omits, what is well known in the art. *Spectra-Physics Inc. v. Coherent Inc.*,827 F.2d 1524 (Fed.Cir. 1987). Therefore, the information disclosed in the Specification is complies with the statutory requirements for definiteness.

Claim 40 is said to be indefinite because "it is not clear what is the reporter gene, what said gene reports and what is the promoter from a TLR-4 gene." However, the term "reporter gene" is well known in the art. "Reporter gene" may be defined as:

> "A coding sequence attached to heterologous promoter or enhancer elements and whose product is easily and quantifiably assayed when the construct is introduced into tissues or cells of the same origin as the regulatory elements. Reporter genes commonly used in the study of eukaryotic gene expression include bacterial genes encoding β-galactosidase (*lacZ*), chloramphenicol acetyltransferase (*cat*) and β-glucuronidase (*gus*)."

Encyclopedia of Molecular Biology, Kendrew (ed.), Blackwell Science Ltd., Oxford (1994), p. 953. One of ordinary skill in the art would readily understand what the term means and how to use a reporter gene in the methods claimed. One of ordinary skill in the art would further understand that "what the reporter gene reports" is expression of the gene of interest. Further, with regard to "promoter from a TLR-4 gene," the Specification discusses promoters at length at page 56, line 26 to page 59, line 2. A list of promoters suitable for use in the present invention is found at pages 60-61 of the Specification.

The Action suggests that claim 62 is indefinite because "it is not clear what are the

'conditions that normally allow for TLR-4 transcription and translation'." However, one of ordinary skill in the art would be well aware of the required conditions. In addition, the Specification provides extensive disclosure on transcription and translation procedures at page 47, line 25 to page 52, line 13 and page 56, line 16 to page 59, line 23.

Claim 69 is said to be indefinite because "it is not clear what is a 'small molecule inhibitor'." The term "small molecule inhibitor" is a term well known and widely used in the art of molecular biology. "That which is common and well known is as if it were written out in the application and delineated in the drawings." *Webster Loom Co. v. Higgins,* 105 U.S. 580 (1882).

The Action suggests that claim 71 is indefinite because "'stimulator of an immune response' does not provide any structural limitations to the modulator." However, the MPEP confirms that there is nothing inherently wrong with defining some part of an invention in functional terms. MPEP 2173.05(g). The Specification discloses "Inhibitors, Stimulators and Screening Assays" at page77, line 26 to page 80, line 28. Specific information is provided at page 79, line 26 to page 80, line 6. The Specification therefore provides adequate information to set definite boundaries on the patent protection sought, as sufficient per MPEP 2173.05(g).

Because the claims from which claims 39, 53-55, 57-61, 65, 66, 68-75, and 100 are definite, these dependent claims are definite as well.

For the above reasons, the claims particularly point out and distinctly claim the subject matter Applicants regard as their invention. Applicants therefore respectfully request the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

E. Conclusion

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims

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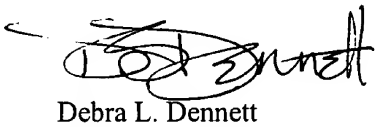
be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,



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